Reviewer's report

Title: Is Inhibition of Kinase Activity the Only Therapeutic Strategy for LRRK2-associated Parkinson's Disease?

Version: 1 Date: 17 November 2011

Reviewer: M Flint Beal

Reviewer's report:

This is a manuscript which reviews therapeutic strategies for treating LRRK2 associated PD. The manuscript is well-written. It focuses on a number of interesting aspects concerning the pathogenesis of LRRK2 induced PD. In particular, it examines recent progress in the development of specific LRRK2 kinase inhibitors. They also discuss a number of other approaches. They review the potential effects of mutations in different sites of the protein. It has been demonstrated that dead versions of mutant LRRK2 are less toxic than kinase active versions of the same proteins. Increased kinase activity has been shown with the G2019S and I2020T mutations. However, this is not universally true. They review the mutations in the ROC domain that prevent GTP binding and the data that GTPase activity regulates kinase activity. It however has been shown that LRRK2 kinase activity is not increased by adding GTP. Another possibility is that the GTP binding mutant disrupted destabilize the ROC with a loss of kinase activity being secondary. There is also some data that LRRK2 can act as a scaffold protein. Interestingly, one of the observations which occurred both in vitro and in vivo was neutrite shortening. The authors discuss other aspects of the function of LRRK2 that could be targeted therapeutically. They review the possibility of LRRK2 kinase inhibition as well as GTPase activity inhibition. They review two recent studies showing that there are compounds that bind selectively to LRRK2 over other kinases. Two of the mutants have been shown to have lower GTPase activity, the R1441C and the Y1699C. They suggest that blocking the GTP binding process of ROC stimulation of GTPase activity might be a worthwhile approach. They then review strategies based outside of the enzymatic regions. One possibility will be to prevent diamerization.

Overall, this is an excellent short review, which covers its topic extremely well. It is concise and up-to-date as well as well-written.